FORMATION OF THIAZOLE AND 1,3-THIAZOLIDINE SULFOXIDE FROM PYROLYSIS OF A THIOLSULFINATE

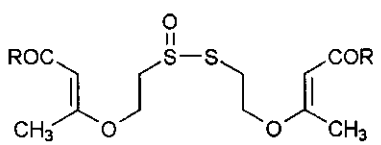
Heduck Mah[+], Kee Dal Nam, and Hoh-Gyu Hahn[*]

Organic Chemistry Lab, Korea Institute of Science and Technology, P. O. Box 131, Cheongryang, 136-791, Seoul, Korea
[+]Department of Chemistry, Kyonggi University, Suwon 440-270, Seoul, Korea

Abstract - The mechanistic study on the pyrolytic transformation of a thiolsulfinate (**2**) is described. The reactive intermediates sulfenic acid (**6**) and thioaldehyde (**8**) were formed resulting from S-S bond cleavage and a hydrogen transfer from sulfenyl to sulfinyl moiety. A stereospecific cyclization of **6** to *cis*-sulfoxide (**4**) was observed, which arouse from the geometrical requirements of a planar transition state for the reacting bonds and atoms in the sigmatropic rearrangement. In the transformation of **8** to thiazole (**9**), the amide carbonyl group facilitated the elimination of a neighboring proton and enabled to furnish the nucleophilic attack of a thiocarbonyl sulfur at β to internal carbonyl group to yield thiazole (**9**).

INTRODUCTION

In our previous paper,[1] we reported that the thermolysis of a thiolsulfinate (**1**) in refluxing benzene or toluene afforded a thiirane and 1,3-oxathiolane sulfoxide *via* thioaldehyde and sulfenic acid intermediates. As an extension of our studies on the reactivity of the thiolsulfinate, we now report the pyrolytic transformation of thiolsulfinate (**2**), an analogue of **1**, and compare the results with those reported.



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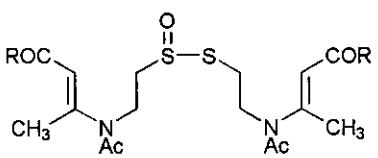


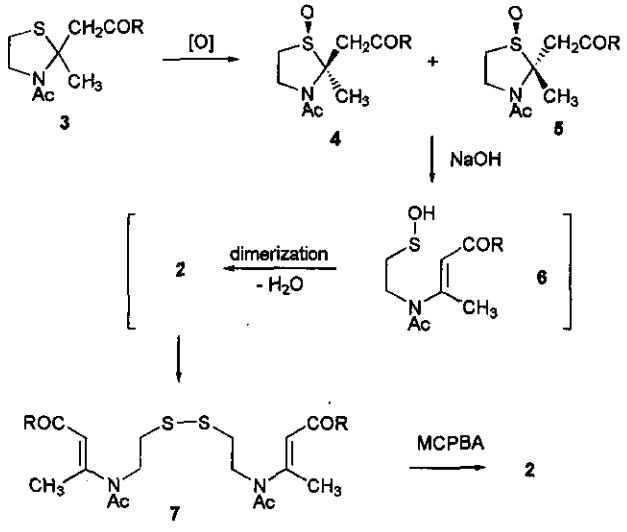
2

R = NHC_6H_5

SYNTHESIS OF THE SULFOXIDES AND THIOLSULFINATES

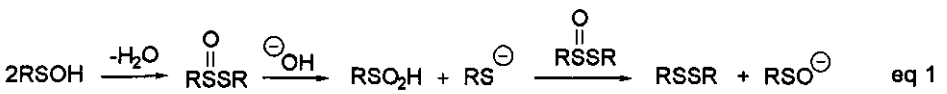
The parent 1,3-thiazolidine sulfoxides (**4**) and (**5**) were prepared by the oxidation of 1,3-thiazolidine (**3**)

(Scheme 1). We arbitrarily named isomer (**4**) as *cis* (when the sulfoxide oxygen and the CH_2COR group are on the same face of the thiazolidine ring) and (**5**) as *trans* (when they are on opposite faces). As *cis*-**4** and *trans*-**5** sulfoxides are diastereomeric, they could be separated either by fractional crystallization or by preparative TLC.[2]



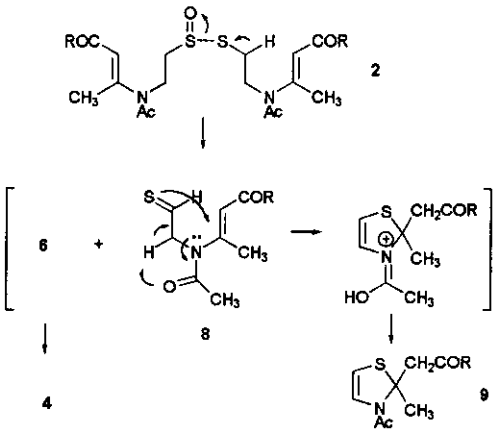
Scheme 1

Without separation of the isomers, treatment of a 3:2 mixture of sulfoxides (**4**) and (**5**) with sodium hydroxide in aqueous methyl alcohol at reflux gave a new disulfide (**7**) in low yield (8.6%). In the presence of sodium hydroxide catalyst both *cis*-**4** and *trans*-**5** sulfoxides readily underwent ring opening by β-elimination upon a carbonyl activated methylene hydrogen abstraction to give the sulfenic acid (**6**). In general, such sulfenic acids are unstable, and dimerize to a thiolsulfinate,[4] which is transformed to a corresponding disulfide, thiosulfonic S-ester and sulfinic acid in the presence of hydroxide ion (eq 1).[5] Similarly, the sulfenic acid (**6**) dimerized to a thiolsulfinate (**2**), which was unstable to disproportionate to give disulfide (**7**). The structure of **7** was confirmed by the spectral techniques and by elemental analysis. In mass spectrum of **7** the molecular ion (M^+) at *m/z* 276 was observed resulting from the cleavage of the labile S-S bond. Although TLC clearly revealed the presence of **2**, it was too scarce to isolate by chromatography. In this reaction, sodium hydroxide attacks the sulfinyl sulfur as a nucleophile, and also abstracts a carbonyl activated hydrogen of the sulfoxide. As expected, the oxidation of disulfide (**7**) with *m*-CPBA gave the thiolsulfinate (**2**) in good yields. The only structural difference between **7** and **2** is a sulfoxide group, which shows a strong absorption band at 1084 cm^{-1} in the IR spectrum.



PYROLYSIS OF THIOLSULFINATE

When the thiolsulfinate (**2**) was refluxed in toluene, a 3:2 mixture of thiazole (**9**), and *cis*-sulfoxide (**4**) was produced as isolable products accompanied with a small amount of a complex mixture.[6] Formation of the *cis*-sulfoxide (**4**) and the thiazole (**9**) strongly suggests that sulfenic acid (**6**) and thioaldehyde (**8**), which are nonisolable reactive intermediates, are generated during the pyrolysis of the thiolsulfinate (**2**) (Scheme 2). In the mass spectrum of **2**, although the molecular ion was not observed, the fragments at *m/z* 294 and 276, resulting from S-S bond cleavage and a hydrogen transfer from sulfenyl to sulfinyl moiety, was seen. This decomposition is due to a weak S-S bond and a labile α-sulfenyl hydrogen, characteristic of a thiolsulfinate.[7]

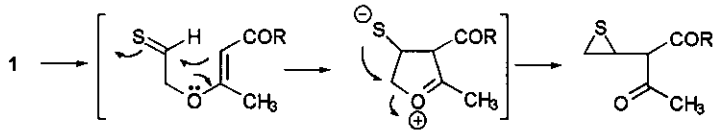


Scheme 2

Stereospecific cyclization of the sulfenic acid (**6**) intermediate to *cis*-sulfoxide (**4**), in which the sulfoxide oxygen and the $CH_2CONHC_6H_5$ group are on the same face of the thiazolidine ring, illustrates a reversal of a previously reported[3] [2,3] sigmatropic ring opening of **4** (Figure 1). This may be a result of the geometrical requirements of a planar transition state for the reacting bonds and atoms in the cyclization.[4]

Figure 1 Stereospecific cyclization of a sulfenic acid (**6**) to a *cis*-sulfoxide (**4**).

Whereas only a few cases of thioaldehyde isolation have been reported,[8] other reports mention the isolation of products which suggest the intermediacy of a thioaldehyde.[9] In case of the thioaldehyde (**8**), however, the amide carbonyl group possibly facilitates the elimination of a neighboring hydrogen to enhance the nucleophilic attack of the thiocarbonyl sulfur that ultimately provides the thiazole (**9**) (see Scheme 2). In comparison, an analogous thioaldehyde (**10**) generated from thiolsulfinate (**1**) to episufide (**12**) possibly through an oxonium ion (**11**) (Scheme 3).[1] This contrasts to the effect of the amide group in **8** that results in the elimination of the neighboring hydrogen to form the thiazole (**9**).



10 **11** **12**

R = NHC_6H_5

Scheme 3

EXPERIMENTAL SECTION

Melting points were determined on a Thomas-Hoover capillary melting point apparatus. All ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer. Chemical shift (δ) are given in ppm and the coupling constants (*J*) in Hz. IR spectra were obtained on a Perkin-Elmer 16F-PC FT-IR and are reported in cm^{-1}. Mass spectra (MS) were recorded on a Hewlet Packard 5890 series GC/MSD. Electron-impact high-resolution mass spectra (HRMS) were obtained on a VG70-VSEQ (VG analytical) high-resolution mass spectrometer at 70eV. Elemental analyses were performed using a Fisons EA1108 analyzer. All chromatographic isolation was accomplished on silica gel GF254 (70-230 mesh).

Preparation of 1,3-Thiazolidine (3)

A solution of acetoacetanilide (51.67 g, 0.292 mol), 2-aminoethanethiol (625 g, 0.324 mol), and *p*-toluenesulfonic acid monohydrate (2.77 g) in benzene (300 mL) was heated at reflux for 6 h with a Dean-Stark water separator and then cooled to rt. The reaction mixture was washed with water and dried over sodium sulfate. The solvent was removed *in vacuo* to give a yellow oily liquid (67.19 g, 98%). This was dissolved in acetic anhydride (121 mL) and stirred for 4 h at rt. The white precipitate which was the thiazolidine (**3**) was collected by filtration (72.5 g, 91%).

mp 197-204 °C (recrystallized from ethanol), ^1H NMR (DMSO-d_6) 1.83 (s, 3H, 2-CH_3), 2.03 (s, 3H, $COCH_3$), 2.95 (t, J = 5.7, 2H, 5-CH_2), 3.15 and 3.24 (2d, AB pattern J = 14.6, 2H, 2-CH_2CO), 3.77-3.85 and 3.88-3.95 (m, 2H, 4-CH_2), 6.98-7.59 (m, 5H, ArH), 9.90 (br s, 1H, NH); ^{13}C NMR (78.5 MHz, DMSO-d_6) 25.44, 27.34, 28.16, 45.00, 53.37, 71.94, 119.11, 123.03, 128.59, 139.09, 167.89, 168.10; MS,

m/z 278 (M^+); IR 1680, 1630.

Anal. Calcd for $C_{14}H_{18}N_2O_2S$, C, 60.41, H, 6.52, N, 10.06. Found, C, 60.22, H, 6.69, N, 10.05.

Preparation of 1,3-Thiazolidine Sulfoxides (4) and (5)

To an ice-cooled solution of 1,3-thiazolidine (**3**) (13.9 g, 50 mmol) and benzeneseleninic acid (90 mg) in methylene chloride (100 mL) was added 35% hydrogen peroxide in water (8 mL, about 80 mmol) dropwise with vigorous stirring at rt. The reaction mixture was stirred for 18 h, washed with saturated sodium bicarbonate solution, cold water, and then dried (Na_2SO_4). The solvent was removed under reduced pressure to obtain a white foamy solid (12.7 g, 86%) consisting of a 3:2 mixture of *cis*-sulfoxide (**4**) and *trans* (**5**)-sulfoxide, which were separated by flash chromatography using 50:1 chloroform-methanol as an eluent.

cis-sulfoxide mp 49-51 °C (recrystallized from methylene chloride and cyclohexane); ^{1}H NMR (DMSO-d_6) 1.60 (s, 3H, 2-CH_3), 2.10 (s, 3H, $COCH_3$), 2.78 and 3.95 (2d, AB pattern, J = 16.6, 2H, 2-CH_2CO), 3.00-3.05 (m, 2H, 5-CH_2), 4.01-4.09 and 4.19-4.23 (2m, 2H, 4-CH_2), 7.00-7.57 (m, 5H, ArH), 10.09 (br s, 1H, NH); IR (KBr) 1670 (C=O), 1625 (C=O), 1040 (S->O); MS, *m/z* 294 (M^+). *Anal.* Calcd for $C_{14}H_{18}N_2O_3S$ C, 57.52, H, 6.10, N, 9.27, S, 10.92. Found, C, 57.2, H, 6.26, N, 9.54, S, 10.8

trans-sulfoxide mp 149.5-150.5 °C (recrystallized from methylene chloride and cyclohexane); ^{1}H NMR (DMSO-d_6) 1.83 (s, 3H, 2-CH_3), 2.03 (s, 3H, $COCH_3$), 2.96 (t, J = 5.5 Hz, 2H, 5-CH_2), 3.13 and 3.31 (2d, AB pattern, J = 14.5, 2H, 2-CH_2), 3.78-3.85 and 3.88-3.95 (2m, 2H, 4-CH_2), 6.99-7.58 (m, 5H, ArH), 9.88 (s, 1H, NH); IR (KBr) 1675 (C=O), 1625 (C=O), 1060 (S->O); MS, *m/z* 294 (M^+). *Anal.* Calcd for $C_{14}H_{18}N_2O_3S$, C, 57.52, H, 6.10, N, 9.27, S, 10.92. Found, C, 57.12, H, 6.16, N, 9.52, S, 10.89.

Preparation of Disulfide (7)

A solution of sodium hydroxide (0.4 g, 10 mmol) and a 3:2 mixture of *cis* (**4**)- and *trans* (**5**)-sulfoxide (29.4 g, 0.1 mol) in methanol (150 mL) was stirred at rt for 12 h. The white precipitate was filtered and washed with a small amount of cold methanol to give a white solid (2.4 g, 8.6%).

mp 202 °C (recrysrallized from ethanol); ^{1}H NMR (DMSO-d_6 + $CDCl_3$) 1.88 (s, 6H, $COCH_3$), 2.00 (s, 6H, CH_3), 2.50-2.97 (m, 4H, SCH_2), 3.42-3.84 (2m, 4H, NCH_2), 6.08 (s, 2H, vinyl CH), 6.94-7.56 (m, 10H, ArH), 9.84 (br. s, 2H, NH); IR (KBr) 3274 (NH), 1684 (C=O); HRMS Calcd for $C_{28}H_{34}N_4O_4S_2$, *m/z* 554.74 (not found), Found *m/z* 276.0925 ($SCH_2CH_2N(COCH_3)CC(CH_3)CHCONHC_6H_5$). *Anal.* Calcd for $C_{28}H_{34}N_4O_4S_2$, C, 60.62, H, 6.18, N, 10.10, S, 11.56. Found, C, 60.70, H, 6.19, N, 9.94, S. 11.70.

Preparation of Thiolsulfinate (2)

To a stirred solution of disulfide (**7**) (0.55 g, 1 mmol) in methanol (10 mL) at 0-5 °C was added dropwise a solution of *m*-CPBA (80-85%, 0.21 g, 1 mmol) in chloroform (10 mL) over 10 min. The cooling bath was removed and the stirring was continued for 2 h at rt. The solvent was removed under the reduced pressure

until only about 30 mL remained, methylene chloride (20 mL) was added and the white precipitate of **2** (0.46 g, 80%) was collected.

mp 169 °C (recrystallized from acetone); ^{1}H NMR (DMSO-d_6 + $CDCl_3$) 3.30 and 3.42 (2s, 6H, 2xCH_3), 3.45 and 3.49 (2s, 6H, $COCH_3$), 4.25-5.60 (m, 8H, SCH_2CH_2N), 7.51 and 7.56 (2s, 2H, vinyl CH), 8.40-8.99 (m, 10H, ArH), 11.40 and 11.44 (br s, 2H, NH); IR (KBr) 3300 (NH), 1682 (C=O); HRMS Calcd for $C_{28}H_{34}N_4O_5S_2$, *m/z* 570.1951 (not found), Found *m/z* 294.1026 ($HOSCH_2CH_2N(COCH_3)CC(CH_3)CHCONHC_6H_5$ and *m/z* 276.0925 ($CHSCH_2N(COCH_3)CC(CH_3)CHCONHC_6H_5$). *Anal.* Calcd for $C_{28}H_{34}N_4O_5S_2$, C, 58.92, H, 6.00, N, 9.82, S, 11.24. Found C, 58.8, H, 6.04, N, 9.54, S, 11.4.

Pyrolysis of Thiolsulfinate (2)

A suspended solution of **2** (0.13 g, 0.23 mmol) in toluene (50 mL) was heated at reflux for 6 h. Evaporation of the reaction mixture gave a light brown oily residue (0.11 g), and this was flash chromatographed using chloroform:methanol = 95:5 as eluent to afford 1,3-thiazole (**9**) (47 mg, 36%) and *cis*-sulfoxide (**4**) (30 mg, 23%).

For 3-acetyl-2,3-dihydro-*N*-phenyl-1,3-thiazole-2-acetamide (**9**)

mp 164-166 °C; ^{1}H NMR ($CDCl_3$) 2.05 (s, 3H, $COCH_3$) 2.12 (s, 3H, 2-CH_3), 3.36 and 3.59 (2d, J = 14.8, AB pattern, 2H, 2-CH_2), 5.62 (d, J = 4.9, 1H, 5-CH), 6.17 (d, J = 4.9, 1H, 4-CH), 7.07-7.51 (m, 5H, ArH), 7.83 (br. s, 1H, NH); IR 1680, 1640, 1600; HRMS Calcd for $C_{14}H_{16}N_2O_2S$, *m/z* 276.0933. Found *m/z* 276.0939. *Anal.* Calcd for $C_{14}H_{16}N_2O_2S$, C, 60.85, H, 5.84, N, 10.14. Found C, 60.60, H, 5.79, N, 9.85.

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